Protein metabolism

سنوات قوية تنتظرك!

ادرس وفكر بطريقة

دخل الشبابتر

أماكن العمليات مهم.

best of luck ✯

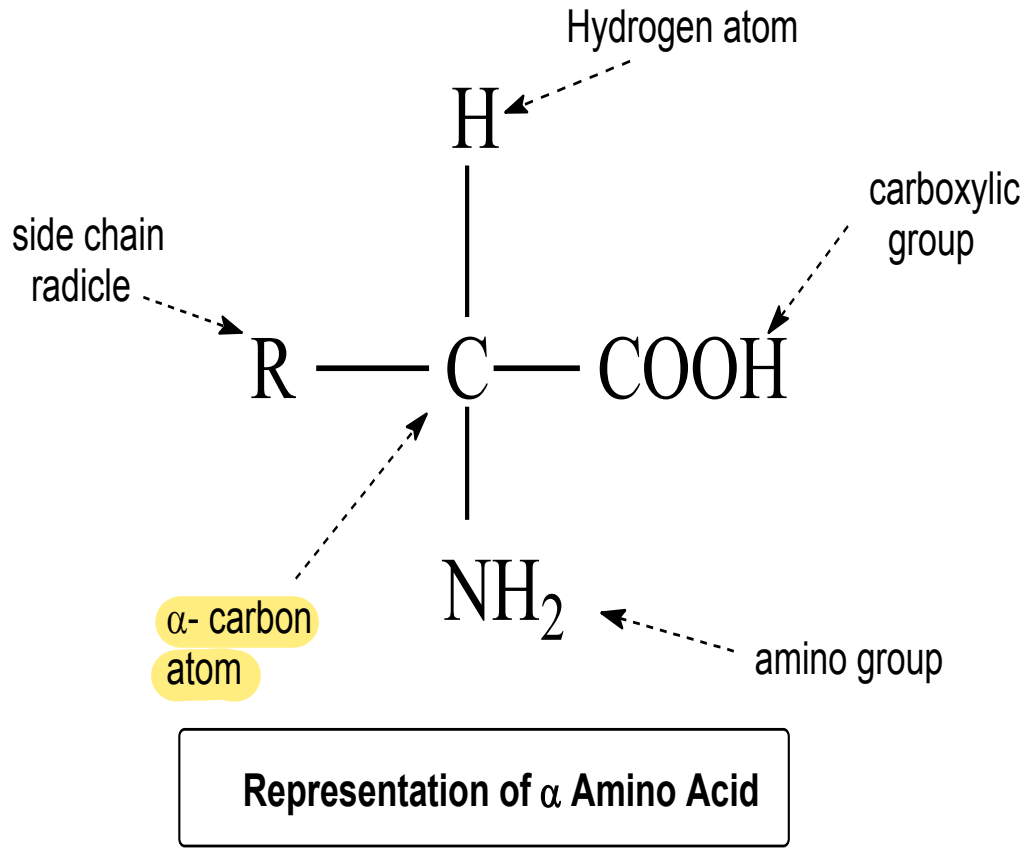
you got this!

Proteins

- **Nitrogen** is a characteristic component of proteins forming about ***16%*** of their weight i.e. 100 g of protein contains 16 g of nitrogen.
- Proteins are not stored in body as such ✓
- Amino acids are degraded by deamination to ammonia and α-ketoacid → continue metabolism; → urea cycle
- Ammonia is used to produce urea and excreted in urine ✓
- α-ketoacid can be metabolized to CO_2 and water, glucose, fatty acid or ketone bodies

- L-a-Amino acids are the structural or the building units of proteins

- The common amino acids have the general structure depicted in the following figure:



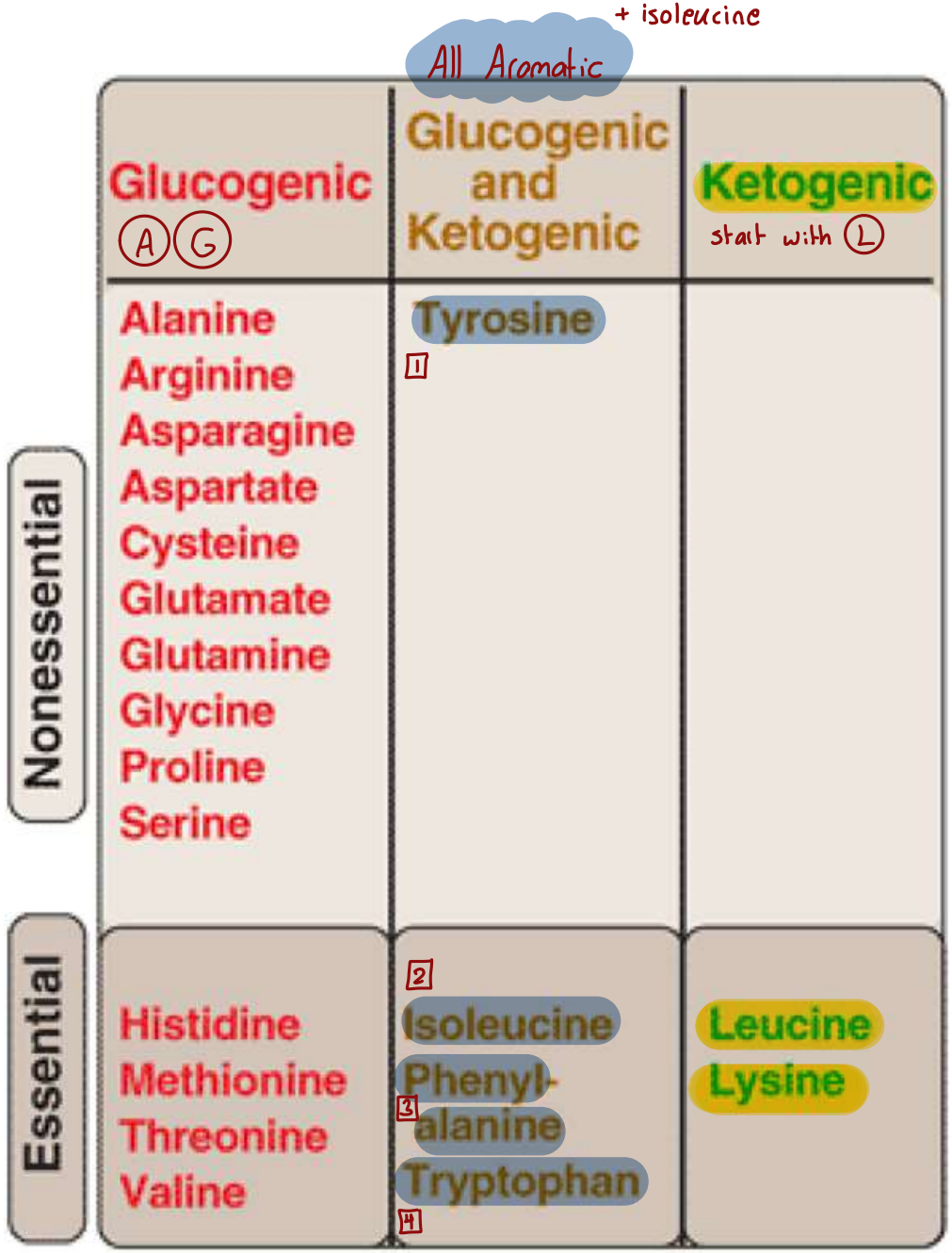
Representation of α Amino Acid

✓ Abbreviations for the 20 Amino Acids

Amino Acid	Abbreviation		**Amino Acid**	Abbreviation	
	Three letter	One letter		Three letter	One letter
Alanine	***Ala***	**A**	Leucine	***Leu***	**L**
Arginine	***Arg***	**R**	Lysine	***Lys***	**K**
Asparagine	***Asn***	**N**	Methionine	***Met***	**M**
Aspartic acid	***Asp***	**D**	Phenylalanine	***Phe***	**F**
Cysteine	***Cys***	**C**	Proline	***Pro***	**P**
Glycine	***Gly***	**G**	Serine	***Ser***	**S**
Glutamine	***Gln***	**Q**	Threonine	***Thr***	**T**
Glutamic acid	***Glu***	**E**	Tryptophan	***Trp***	**W**
Histidine	***His***	**H**	Tyrosine	***Tyr***	**Y**
Isoleucine	***Ile***	**I**	Valine	***Val***	**V**

Metabolic Classification of Amino Acids

glucose الوحيدين إلي ما أقدر أصنع منهم Leucine + Lysine



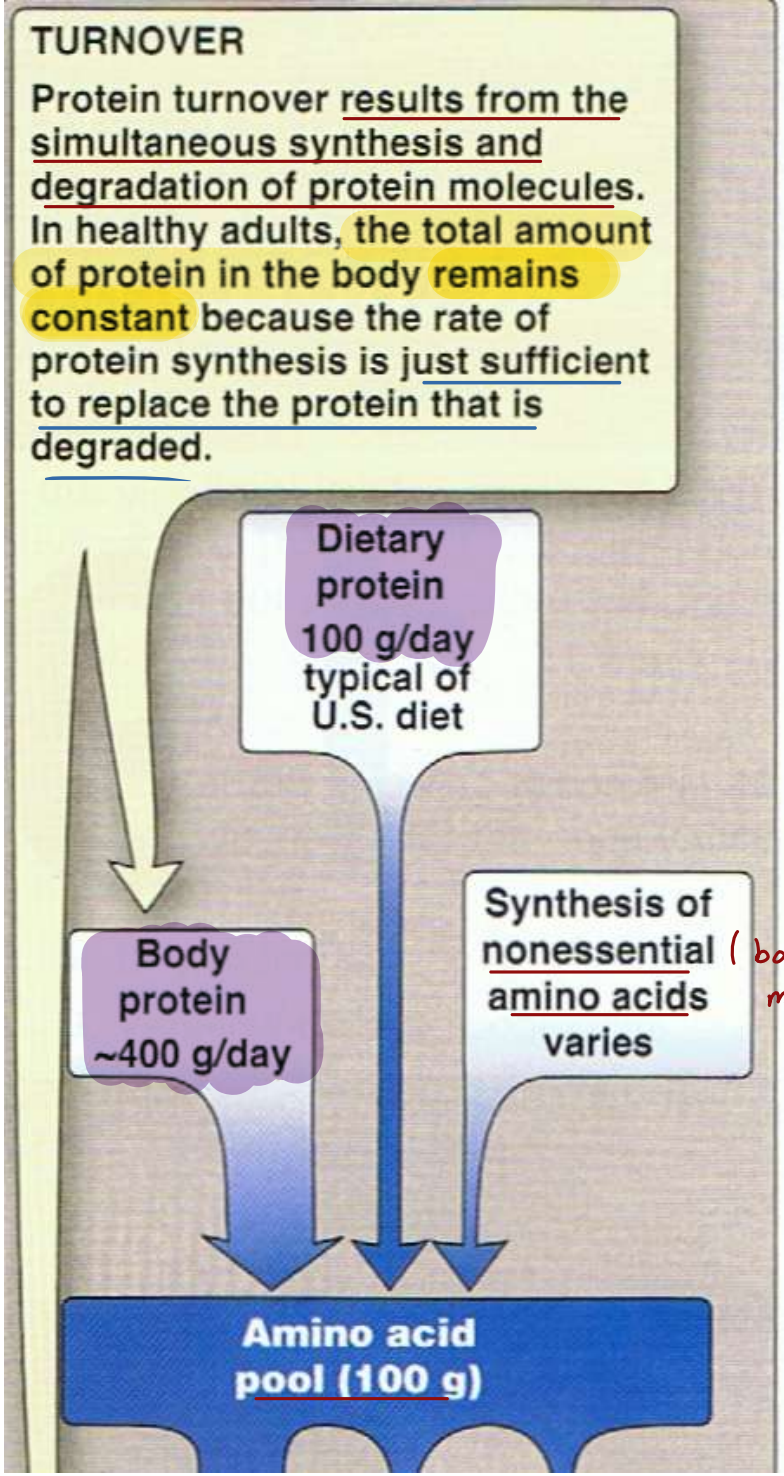
Which of the following amino acids is essential ketogenic:

1. Leucine
2. Alanine
3. Asparagine
4. Glutamate
5. Serine

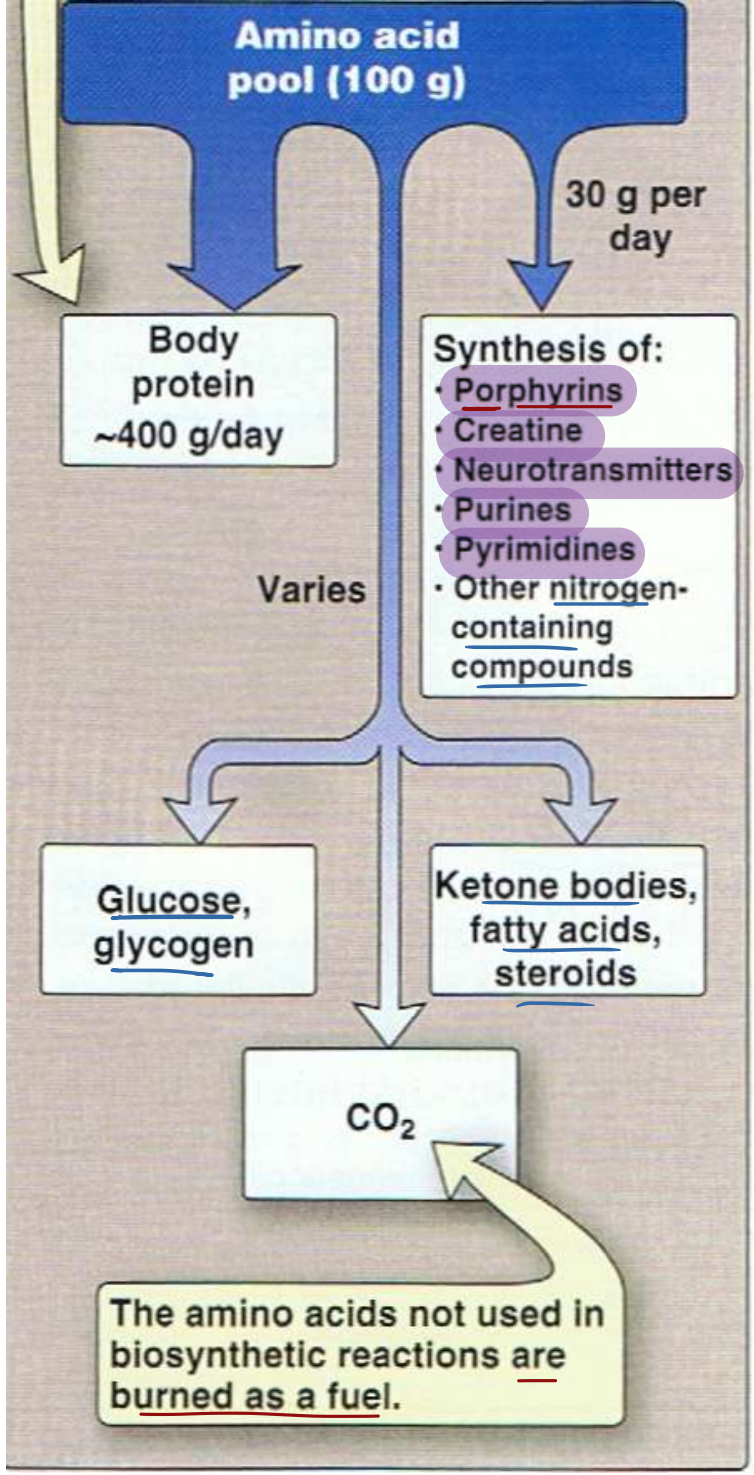
Amino acid metabolism

- Amino acid pool:
  - There is about 12 kg of protein in 70 kg man
  - 75% of aa are used in synthesis of new tissue proteins
  - The remainder is used as precursor for synthesis of many substances

- Protein turnover:
  - Proteins are constantly degraded and synthesized which is regulated by the concentration of protein in the cell
  - 300-400 g of proteins are hydrolyzed and resynthesized/day
  - Protein turnover varies: short lived (regulatory and misfolded proteins), long-lived (most of tissue proteins) and structurally stable (collagen)



(body can make it)



* I can't synthesize glucose from "fatty acids" just from "glycerol"

Nitrogen Balance

- anabolic state -

- **Positive Nitrogen Balance means N2 intake is more than N2 output:** إلي دخل أكتر من إلي طلع لأنه بنبني فيه و نستخدمه
- This exists when intake of N2 exceeds the output. It occurs whenever new tissues are being built up for example:

1- During growth (growing children).
2- Pregnancy.
3- Muscular training.
4- Convulsions from different diseases.
تشنجات

Nitrogen Balance

catabolic state

B. Negative Nitrogen Balance: N_2 Output is more than N2 intake:

- It occurs in cases of : follow logic

  1- Decreased protein intake: e.g. starvation, malnutrition and G.I.T. diseases. (malabsorption)

  2- Increased Loss of proteins: e.g. in chronic hemorrhage, albuminuria and Lactation on an inadequate protein diet.

  3- Increased of protein catabolism: e.g. fever, hyperthyroidism, diabetes mellitus, Cushing syndrome, advanced cancer and post-surgical.

- Prolonged periods of negative nitrogen balance are dangerous and may lead to death.

Which produces positive nitrogen balance:

1. Diabetes Mellitus
2. Growing children
3. Albuminuria
4. Hyperthyroidism
5. Starvation

Positive Nitrogen :
Muscle training
DM
Albuminuria
All choices

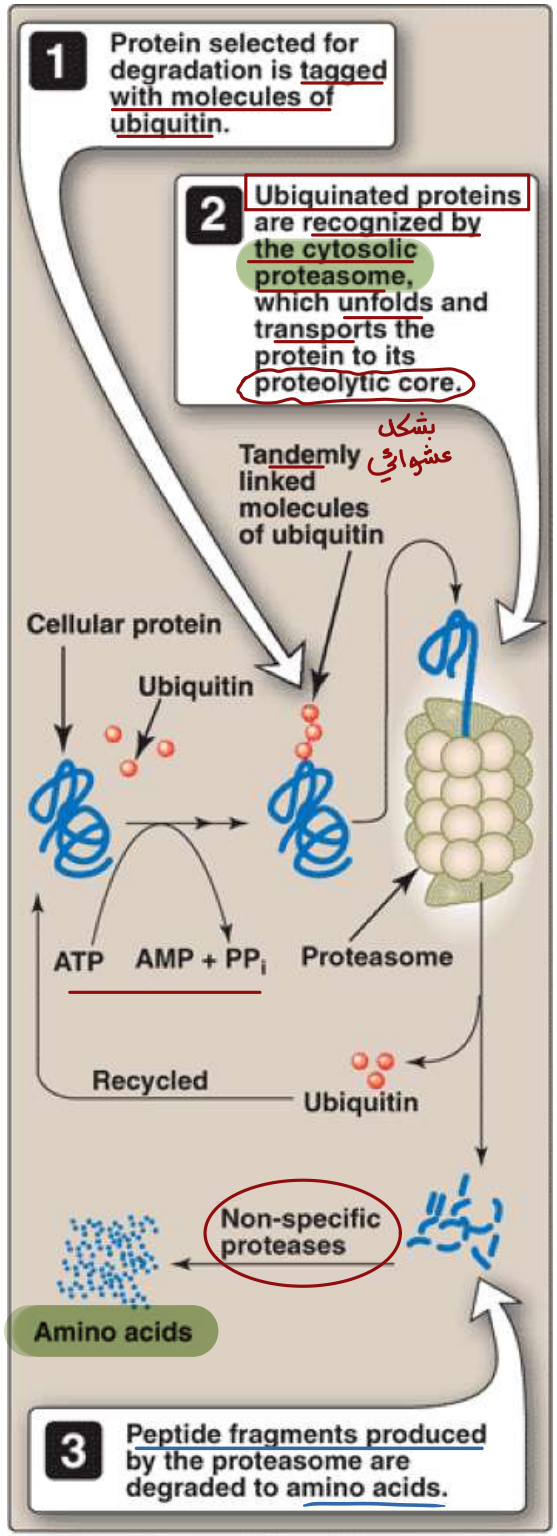
الجواب ١

ubiquitination
labeling زي كعك
for proteins that
need to be degraded

Protein metabolism

- Protein degradation occurs by:
  - energy dependent ubiquitin-protesome mechanism (endogenous proteins)
  - non-energy dependent lysosomes (extracellular protein)
- Oxidized or ubiquitin tagged proteins are preferentially degraded
- Certain aa sequences:
  - Serine (S)at N-terminal: long t1/2 (>20 hr)
  - Aspartate (D) at N-terminal: short t1/2 (3 min)
  - Proteins rich in the sequence (PEST) are rapidly degraded

proline
glutamic acid
therionine
Serine



https://youtu.be/x-1yifFU1r8?si=BCkQ_GfFk04z-ydV

wonderful explination

Digestion of proteins

- protein is antigenic i.e. able to stimulate an immunologic response. The digestion of protein destroys its antigenecity. So, proteins must be digested into amino acids:

1) In the stomach :

A- gastric acid: denature the protein

B- Pepsin: is the major proteolytic enzyme in the stomach :

" protease "

- Pepsin is produced and secreted by the chief cells of the stomach as the inactive zymogen, pepsinogen, which activated by HCl produced by parietal cells of stomach.
- Pepsin catalyzes the cleavage of proteins into smaller polypeptides.

2) in small intestine: large polypeptides are further cleaved to oligopeptides and amino acids by a group of pancreatic proteases.

Each of these enzymes has a different specificity (trypsin cleaves only at C-terminal of arginine or lysine).

Activation of zymogens: Enteropeptidase converts the pancreatic trypsinogen to trypsin which starts a cascade of proteolytic activity, because trypsin is the activator of all the pancreatic zymogens

inactive form of enzyme

جابت سؤال عن trypsinogen انه يتفعل بسبب وجود HCL وكان من ضمن سؤال ايش الخطأ

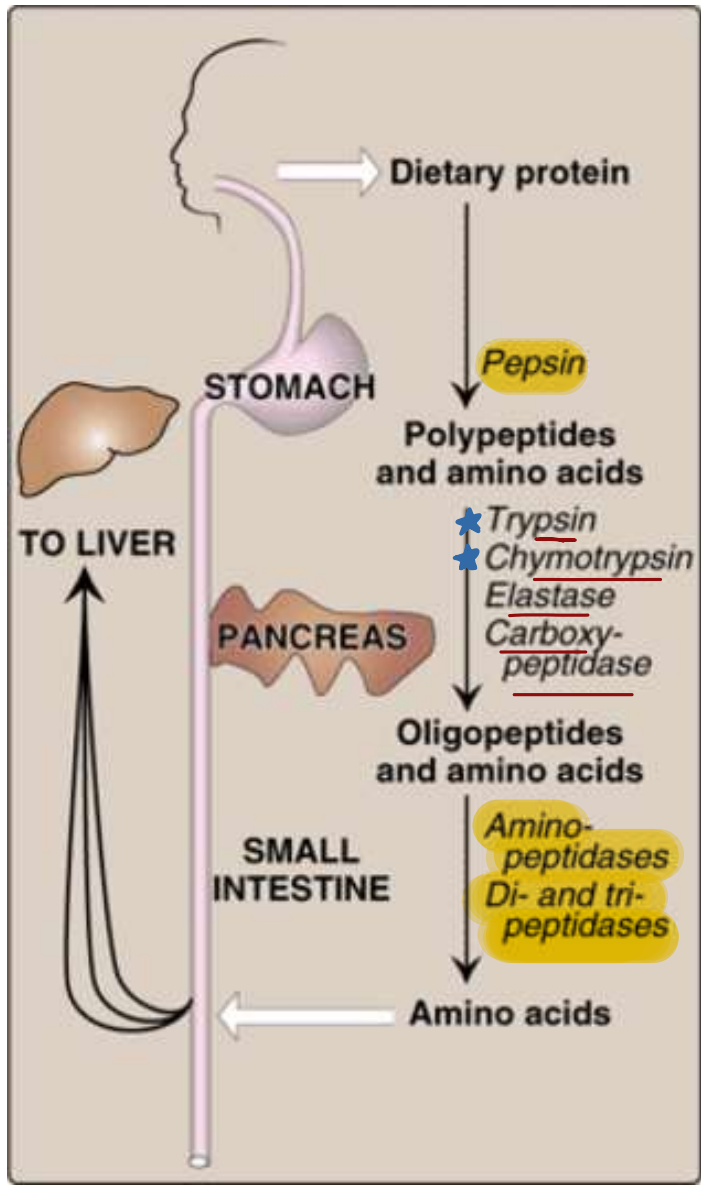
at C-terminal of arginine or lysine).

Activation of zymogens: Enteropeptidase converts the pancreatic trypsinogen to trypsin which starts a cascade of proteolytic activity, because trypsin is the activator of all the pancreatic zymogens

Digestion of proteins

Abnormalities in protein digestion:

- In individuals with a deficiency in pancreatic secretion (chronic pancreatitis, cystic fibrosis, or surgical removal of the pancreas), the digestion and absorption of fat and protein is incomplete.
- This results in the abnormal appearance of lipids (Steatorrhea) and undigested protein in the feces.



Digestion of oligopeptides by enzymes of the small intestine

- The luminal surface of the intestine contains **aminopeptidase** (an exopeptidase that repeatedly cleaves the N-terminal residue of oligopeptides to produce free amino acids and smaller peptides.

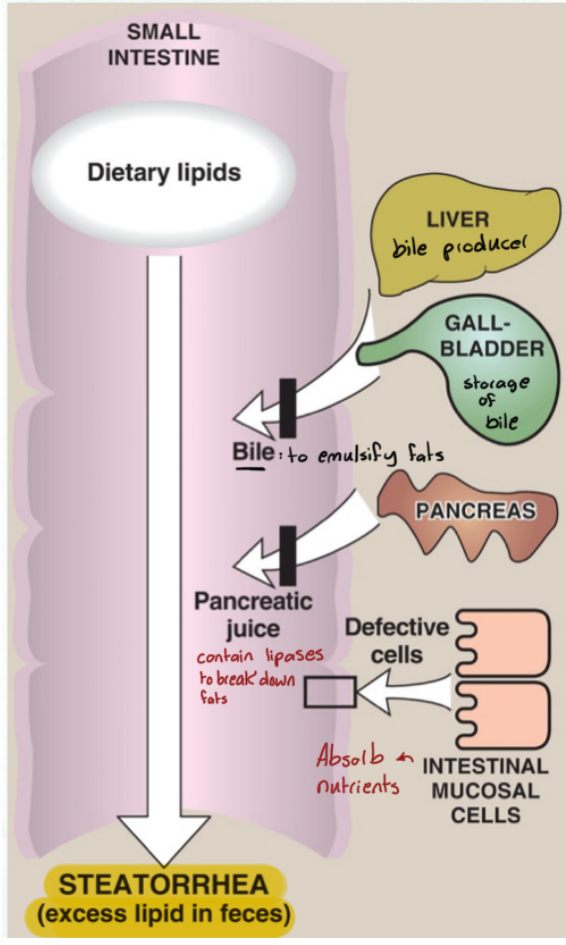
If you would like to remember ☆

سوء امتصاص

Lipid malabsorption (Steatorrhea)

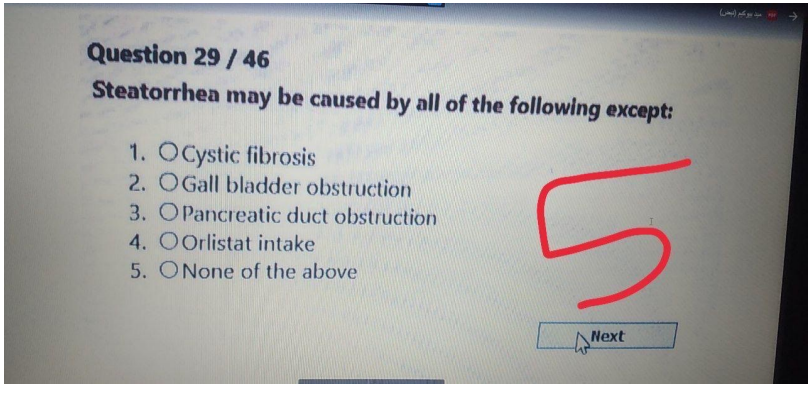
- Cystic fibrosis — No pancreatic juice
- Shortened bowl — low surface area ↓ for absorption

Both causes decrease in absorption of lipids (including fat soluble vitamins and essential fatty acids) leading to increase in lipids in feces (Steatorrhea)



B. Cystic fibrosis

CF is the most common lethal genetic disease in Caucasians of Northern European ancestry and has a prevalence of ~1:3,300 births in the United States. CF is an autosomal-recessive disorder caused by mutations to the gene for the CF transmembrane conductance regulator (CFTR) protein that functions as a chloride channel on epithelium in the pancreas, lungs, testes, and sweat glands. Defective CFTR results in decreased secretion of chloride and increased uptake of sodium and water. In the pancreas, the depletion of water on the cell surface results in thickened mucus that clogs the pancreatic ducts, preventing pancreatic enzymes from reaching the intestine, thereby leading to pancreatic insufficiency. Treatment includes replacement of these enzymes and supplementation with fat-soluble vitamins. [Note: CF also causes chronic lung infections with progressive pulmonary disease and male infertility.]



Orlistat (antiobesity drug) inhibits gastric and pancreatic lipase and so decrease the absorption of fat (also the fat soluble vitamins)

AKED

Absorption of amino acids and dipeptides

- Free amino acids and dipeptides are taken up by the intestinal epithelial cells.
- the dipeptides are hydrolyzed in the cytosol to amino acids before being released into the portal system (only free amino acids are found in the portal vein)
- The absorption of amino acid is active process that needs energy (ATP).

Transport of aa to the cells

SGLT

- Amino acids are transported to the cells by active transport systems, driven by the hydrolysis of ATP

7

- At least seven different transport systems are known that have overlapping specificities for different amino acids.

- For example, one transport system is responsible for reabsorption of the amino acids cystine, ornithine, arginine, and lysine in kidney tubules.

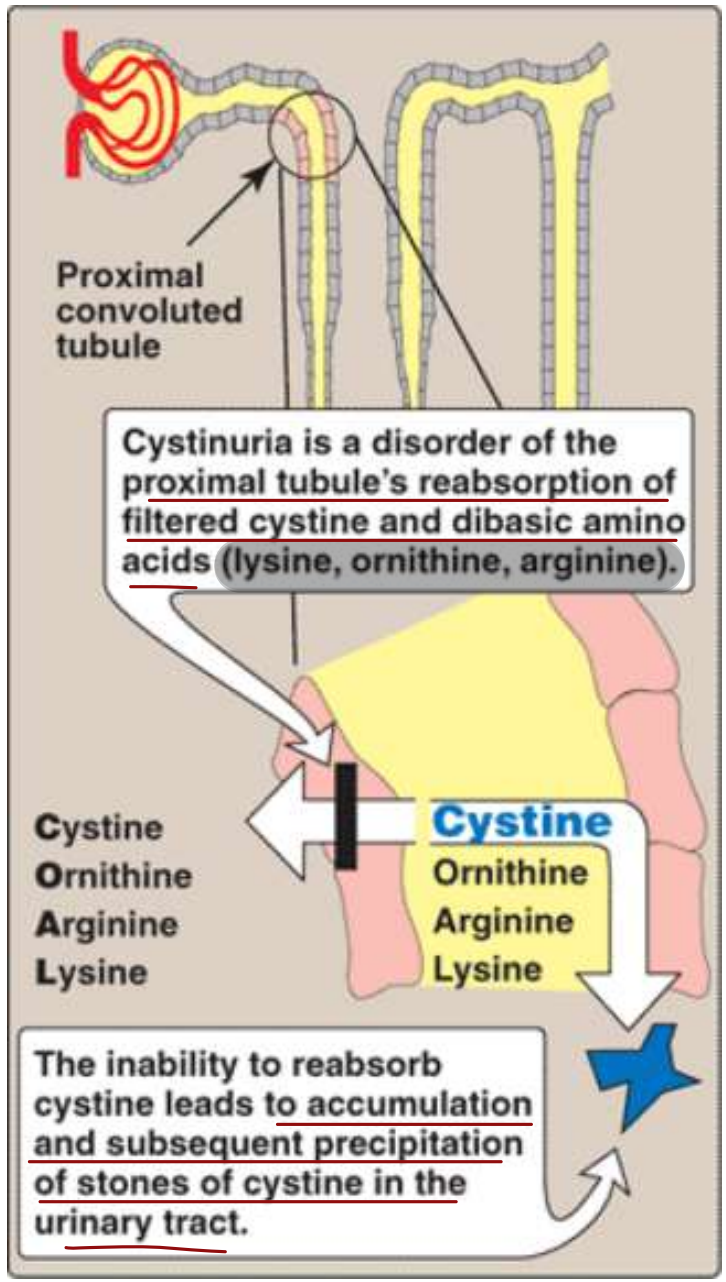
"COLA"

Basic amino acids

Cystinuria

cystine in urine

- In the inherited disorder **cystinuria**, this carrier system is defective, resulting in the appearance of all four amino acids in the urine.
- Cystinuria is the most common genetic error of amino acid transport.
- The disease expresses itself clinically by the precipitation of cystine to form kidney stones (calculi) that may block the urinary tract.
- Oral hydration is important in treatment for this disorder



Removal of nitrogen from aa

transfer of amino groups
- transamination
- oxidative deamination

- Removing the α-amino group is essential for producing energy from any amino acid
- transamination and oxidative deamination reactions which provide ammonia and aspartate, the two sources of urea nitrogen
- The first step is transfer their α-amino group to α-ketoglutarate to produce an α-ketoacid and glutamate.
- Glutamate produced by transamination can be oxidatively deaminated or used as an amino group donor in the synthesis of nonessential amino acids.

Transamination

- The transfer of amino groups from one carbon skeleton to another is catalyzed by a family of enzymes called **aminotransferases**.

- These enzymes are found in the cytosol of cells throughout the body (especially the liver, kidney, intestine, and muscle).

All but KT

- All amino acids (except lysine and threonine) participate in transamination at some point in their catabolism.

- Lysine and threonine lose their α-amino groups by deamination

All amino acids → transamination

Lysine + therionine → Deamination

KT

https://youtu.be/IlnI5-08U8E?si=EnDVUQG0IYEJp-g4

Aminotransferases

- Each aminotransferase is specific for one or, at most, a few amino group donors and named after that enzyme
- Alanine aminotransferase (ALT): enzyme catalyzes (reversibly) the transfer of the amino group of alanine to α-ketoglutarate, resulting in the formation of pyruvate and glutamate.
- Aspartate aminotransferase (AST) is During amino acid catabolism, AST transfers amino groups from glutamate to oxaloacetate, forming aspartate, which is used as a source of nitrogen in the urea cycle
- All aminotransferases require the coenzyme pyridoxal phosphate

vitamin B6

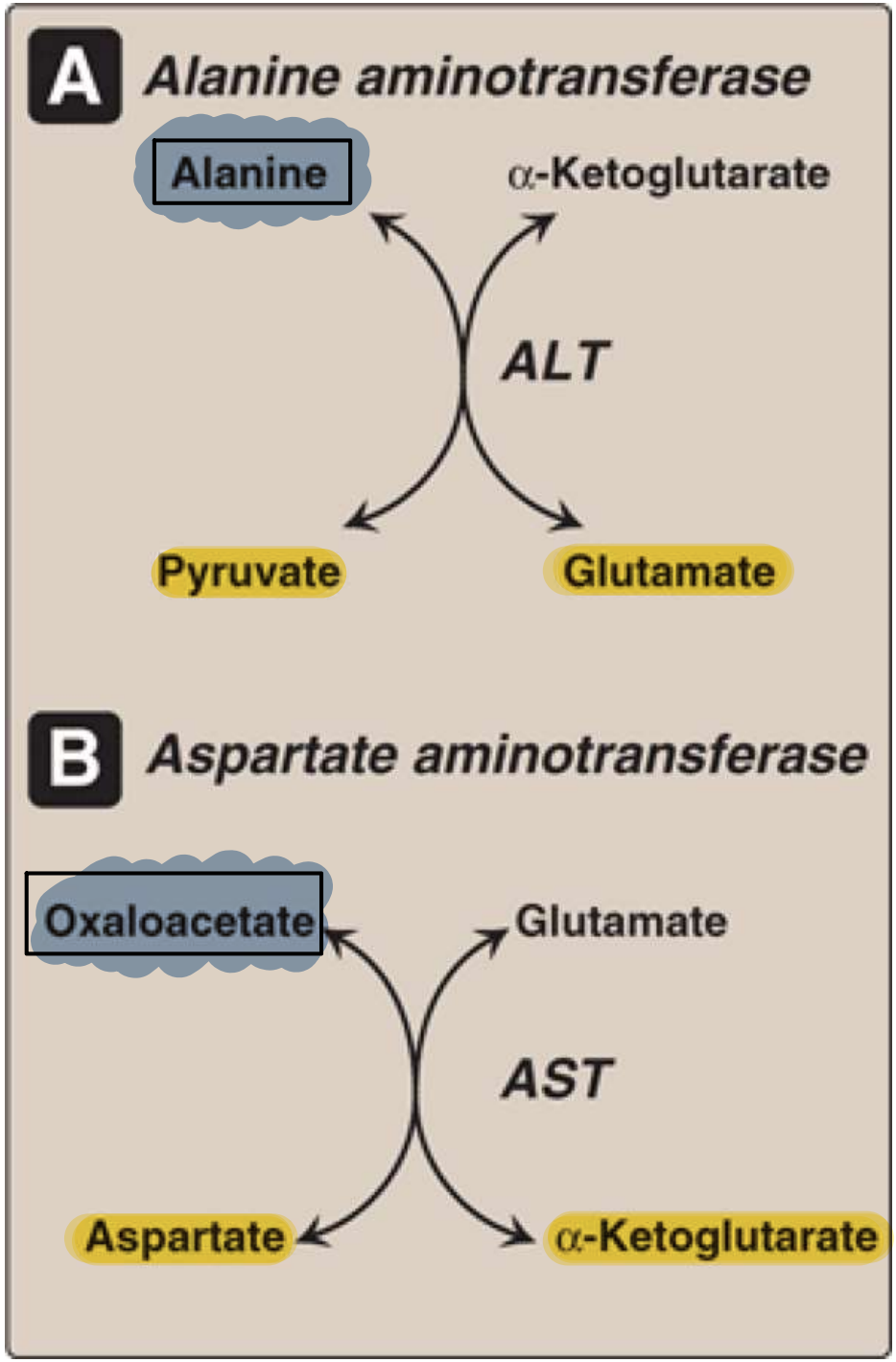
Shortening of the chains: rate limiting enzyme
α(1-4) is cleaved by **glycogen phosphorylase** until four glycosyl units remain on each chain before branch point
The enzyme utilize pyridoxal phosphate which is required as coenzyme
(vitamin B6)

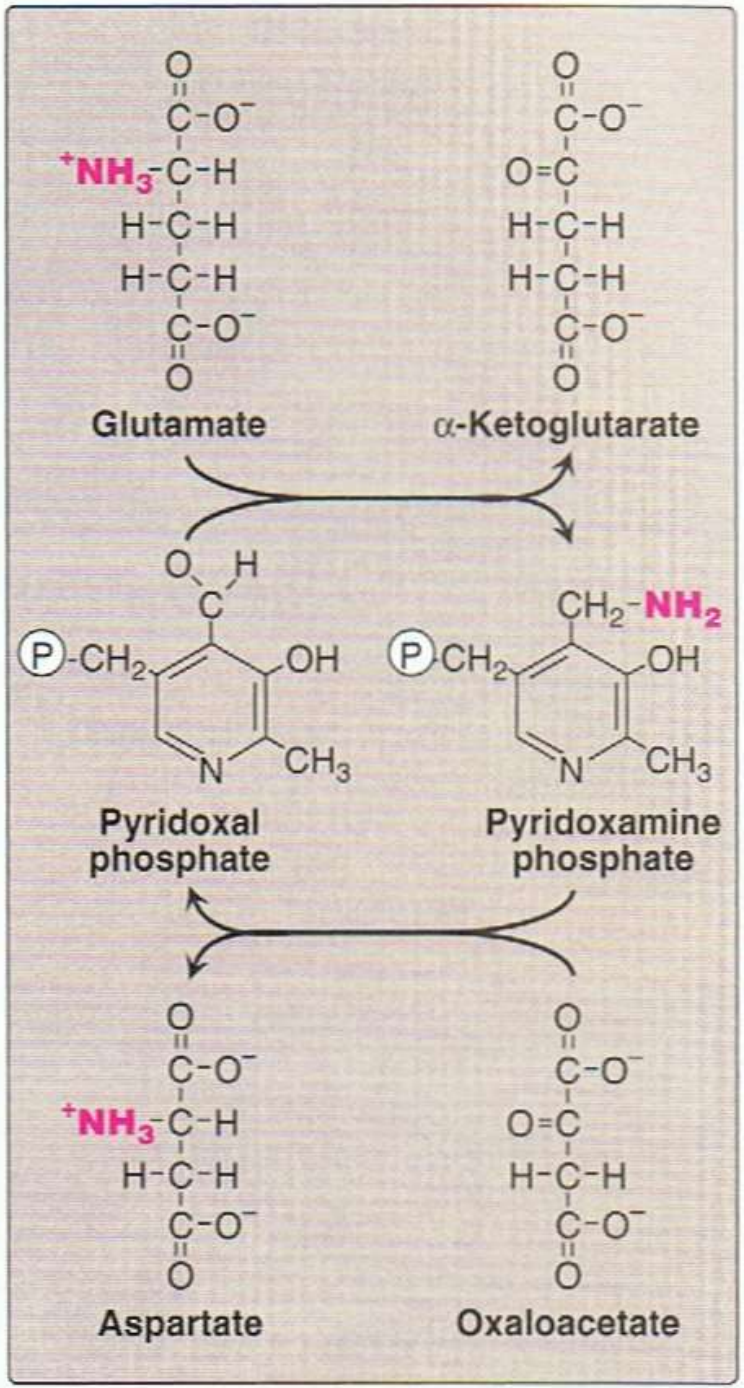
pyridoxal phosphate as a coenzyme جابت ايش الانزيمات يلي بتحتاج ال

two choices الجواب

Glycogen phosphorylase and aminotransferase

Oxaloacetat + glutamate :
Asprtate


A
Alanine aminotransferase
Alanine
α-Ketoglutarate
ALT
Pyruvate
Glutamate
B
Aspartate aminotransferase
Oxaloacetate
Glutamate
AST
Aspartate
α-Ketoglutarate


Glutamate
α-Ketoglutarate
Pyridoxal phosphate
Pyridoxamine phosphate
Aspartate
Oxaloacetate

Diagnostic value of plasma aminotransferases

- Aminotransferases are normally intracellular enzymes, (low levels in the plasma)

- The presence of elevated plasma levels of aminotransferases indicates damage to cells rich in these enzymes. Two aminotransferases (AST and ALT) are of particular diagnostic value when they are found in the plasma.

For example, the enzyme alanine aminotransferase (**ALT**) is abundant in the liver. The appearance of elevated levels of ALT in plasma signals possible damage to **hepatic tissue**.

a. hepatic disease: Plasma AST and ALT are elevated in nearly all liver diseases, specially in extensive cell necrosis (severe viral hepatitis, toxic injury, and prolonged circulatory collapse).

Elevated serum bilirubin results from hepatocellular damage that decreases the hepatic conjugation and excretion of bilirubin

↓ hepatic conjugation
↓ bilirubin excretion

b. Nonhepatic disease: Aminotransferases may be elevated in nonhepatic disease (myocardial infarction and muscle disorders) but those can be clinically distinguished.

glutamate ⟶ (NH_3) α-Ketoglutarate

Glutamate dehydrogenase
(the oxidative deamination of amino acids)

- It is the transfer amino groups from glutamate, oxidative deamination, by glutamate dehydrogenase results in the liberation of the amino group as free ammonia. NH_3 for urea cycle

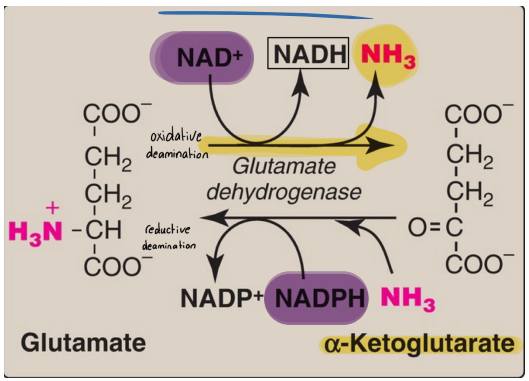
- occur primarily in the liver and kidney.

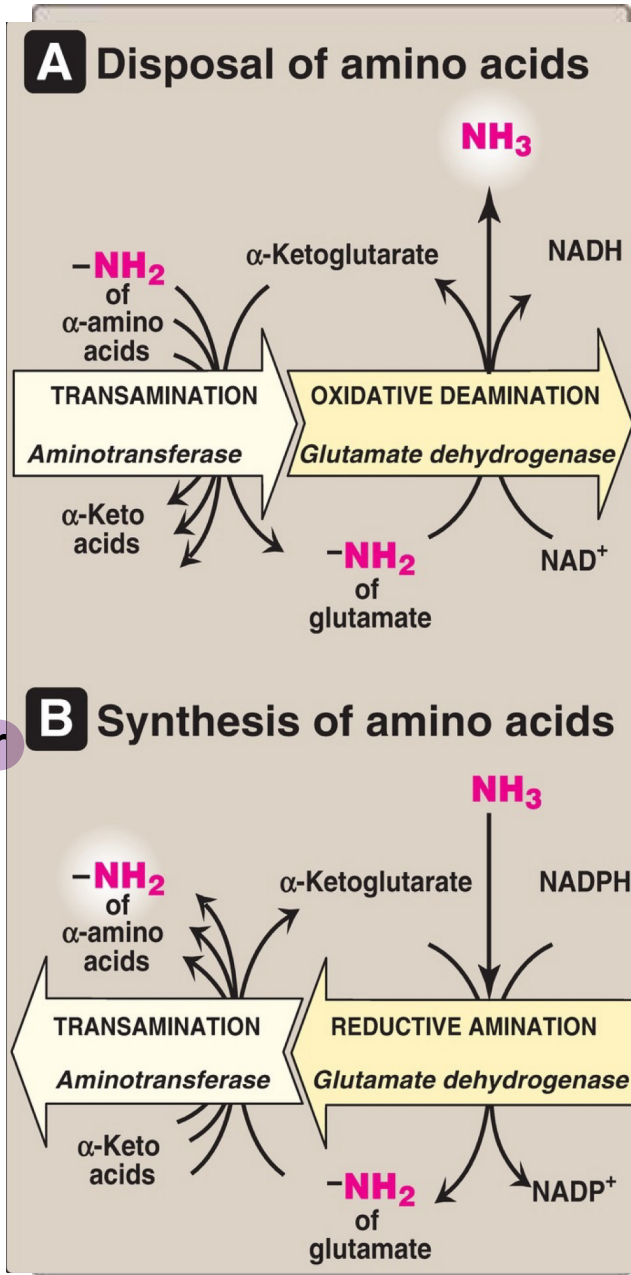
- Glutamate is unique in that it is the only amino acid that undergoes rapid oxidative deamination

- Glutamate dehydrogenase can use either NAD or NADP as a coenzyme. NAD is used primarily in oxidative deamination and NADPH is used in reductive amination

NAD^+ oxidative deamination

$NADP^+$ reductive amination





ATP / GTP
inhibit it

stimulated منطقي لأنه لما يكون α-Ketoglutarate كتير رح يصنع و يدخل
↑ ATP و يصنع Krebs cycle

Glutamate dehydrogenase

- The direction of the reaction depends on the relative concentrations of glutamate, α-ketoglutarate. and ammonia, and the ratio of oxidized to reduced coenzymes.

- After ingestion of a meal containing protein, glutamate levels in the liver are elevated and enhance amino acid degradation and the formation of ammonia

protein ↑ – glutamate ↑ → a.a degradation ↑ – NH_3 formation ↑

- The reaction can also be used to synthesize amino acids from the corresponding α-ketoacids

- ATP and GTP are allosteric inhibitors of glutamate dehydrogenase, whereas ADP and GDP are activators of the enzyme.

most amino acids in human body are in L-form

D-amino acid → α-Ketoacid + NH_3

dependent on FAD

D-Amino acid oxidase

liver

can't be used for protein synthesis

- D-Amino acids are present in the diet, and are efficiently metabolized by the liver using D-Amino acid oxidase (FAD-dependent enzyme) that catalyzes the oxidative deamination of these amino acid isomers.

- The resulting α-ketoacids can enter the general pathways of amino acid metabolism, and be reaminated to L-isomers, or catabalized for energy.

(transamination) → L-amino acid

One-line exam summary

D-amino acid oxidase is an FAD-dependent liver enzyme that performs oxidative deamination of dietary D-amino acids to form α-keto acids, which can be converted to L-amino acids or used for energy.

في ثلاث انزيمات موجودين بالجسم فقط بالكبد
يعني exclusively in liver

Arginase
Glucerol kinase
D amino acid oxidase

كثير مهمين هضول تجميعة من المادة كاملة مش
بس بشابتر واحد وغالبا بتسأل عنهم بكل امتحان

مو عارفة ازا صح متزكرة السؤال
بس كانه جابت ايش الانزيم يلي ما بكون بالكبد
1)arginase only liver
2)a 7 hydroxylase only liver →
3)glycerol kinase liver
4) انزيم غريب ناسية اسمه بس حطيته هو

The rate-limiting step in bile acid synthesis is the introduction of a hydroxyl group at carbon 7 of the steroid nucleus by cholesterol-7-α-hydroxylase, an ER-associated cytochrome P450 (CYP) enzyme found only in liver

1y Like Reply

[redacted]
[redacted] HMG enzyme?

ملخص الاسئلة بالسلايد التاني

toxic

Transport of ammonia from tissues to the liver

There are two mechanisms: → transport as glutamine (most tissues) / → transport as Alanine (mostly muscles)

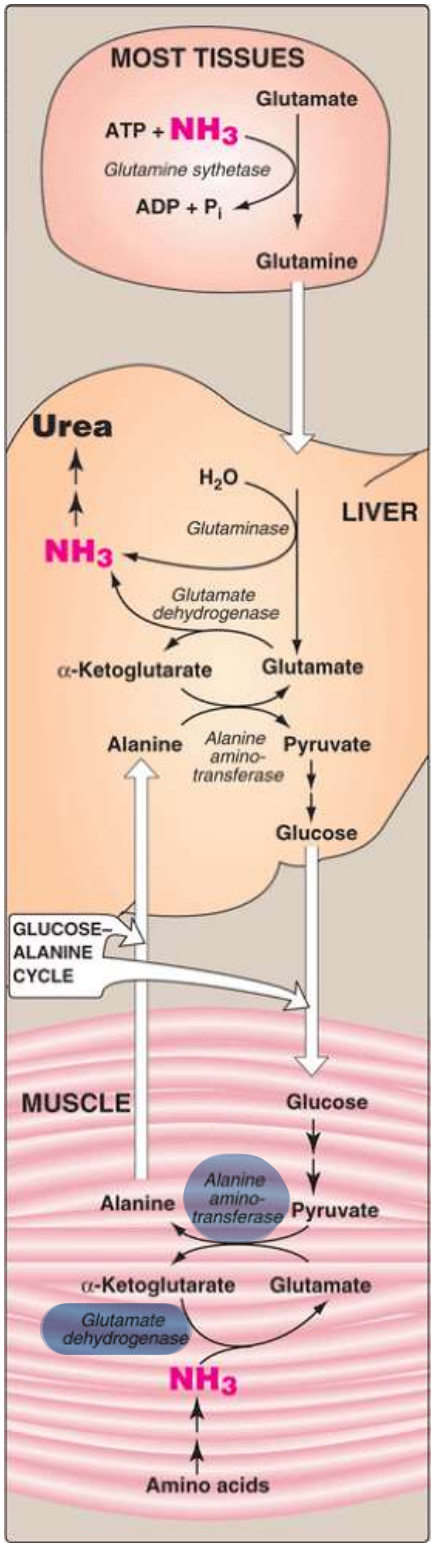
- found in most tissues, uses glutamine synthetase to combine ammonia with glutamate to form glutamine (a nontoxic transport form of ammonia)

The glutamine is transported in the blood to the liver where is cleaved by glutaminase to produce glutamate and free ammonia

NH_3

- used primarily by muscle, involves transamination of pyruvate (the end-product of aerobic glycolysis) to form alanine

Alanine is transported by the blood to the liver, where it is converted to pyruvate, again by transamination (pyruvate is used in gluconeogenesis). This pathway called the **glucose-alanine cycle**.



Ammonia transport

As glutamine (most tissues)

- glutamine synthetase — "non toxic"
  - ↳ combines NH_3 + glutamate $\xrightarrow{+ATP}$ glutamine
- glutaminase
  - ↳ removes NH_3 again

Ammonia is free to enter urea cycle

As Alanine (mostly muscle)

In fasting / exercise

"glucose Alanine cycle"

Alanine transaminase

↳ pyruvate + glutamate (a.a) → Alanine + α-Ketoglutarate

α-Ketoglutarate ↓ undergoes transamination

Alanine → pyruvate

Feature	Glutamine pathway	Alanine pathway
Main tissues	Most tissues	Muscle
Transport form	Glutamine	Alanine
Main purpose	Safe ammonia transport	Ammonia transport + glucose production
Key enzyme	Glutamine synthetase	ALT
Liver enzyme	Glutaminase	ALT
Uses ATP?	Yes	No direct ATP in transamination

سألت عن الشكلين الي ينتقل فيهم الامونيا

C) Transport of ammonia from tissues to the liver

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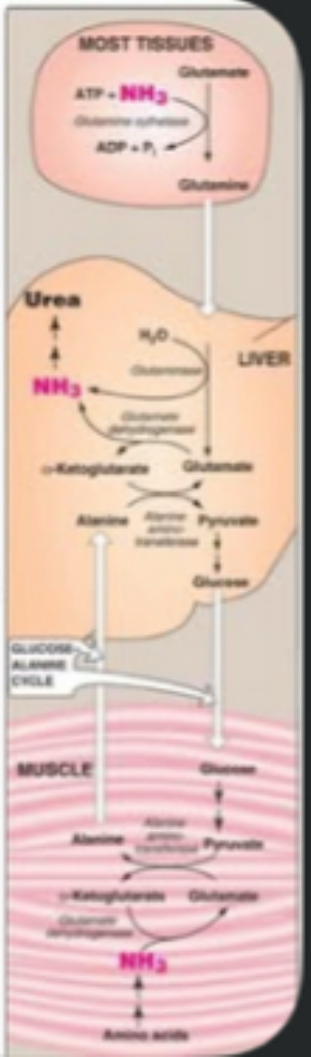
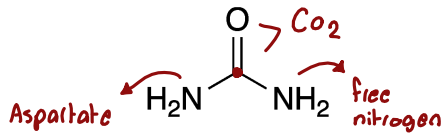


https://youtu.be/XZEJ5PNvjkk?si=WLl_Nvh9vZXC57wA

UREA CYCLE

- Urea is the major disposal form of amino groups derived from amino acids (90% of the nitrogen-containing components of urine).

- One nitrogen of the urea molecule is supplied by free NH3, and the other nitrogen by aspartate, the carbon and oxygen of urea are derived from CO2.



- Urea is produced by the liver, and then is transported in the blood to the kidneys for excretion in the urine.

- Reactions of the cycle:

1. Formation of carbamoyl phosphate by carbamoyl phosphate synthetase I (CPS-1) which requires 2 ATP. N-acetylglutamate is required as allosteric activator.

UREA CYCLE

2. Formation of citrulline: Ornithine and citrulline are basic amino acids that participate in the urea cycle (But not into cellular proteins, no codons). citrulline is transported to the cytosol.

3. Citrulline condenses with aspartate to form argininosuccinate. The α-amino group of aspartate provides the second nitrogen that is ultimately incorporated into urea, which is driven by the cleavage of ATP to AMP and pyrophosphate (PPi).

4. Argininosuccinate is cleaved to yield arginine and fumarate. The arginine formed by this reaction serves as the immediate precursor of urea. Fumarate can reenter the TCA cycle

5. Cleavage of arginine to ornithine and urea by **arginase** occurs almost exclusively in the liver, whereas other tissues (kidney), can synthesize arginine by these reactions

Which of the following is basic amino acid:

1. ○ Ornithine ✓
2. ○ Citrulline
3. ○ Glycine
4. ○ Carnitine
5. ◉ None of the choices

1

Next

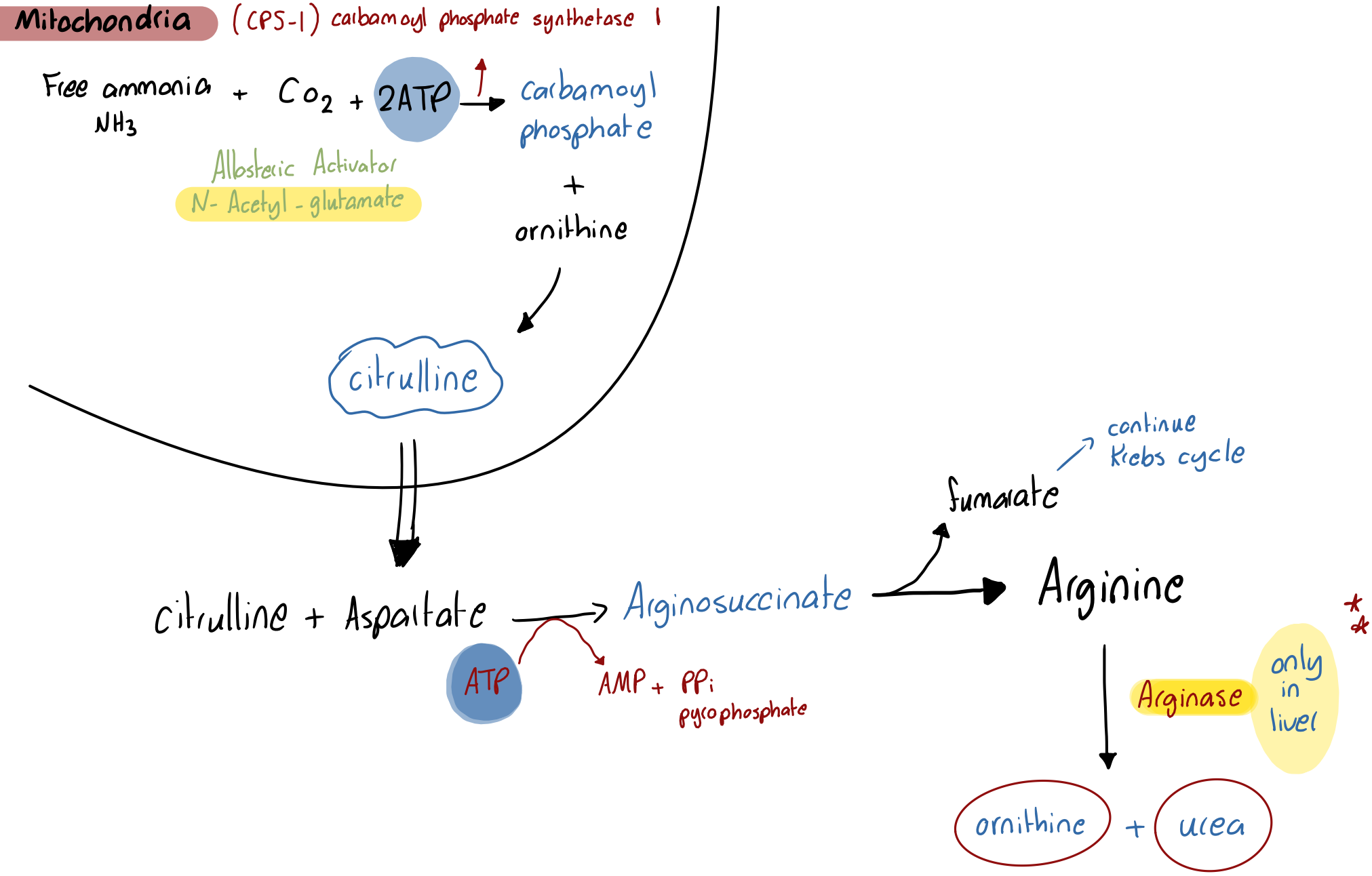
UREA CYCLE

✓ 6. Fate of urea: Urea diffuses from the liver, and is transported in the blood to the kidneys, where it is filtered and excreted in the urine.

A portion of the urea diffuses from the blood into the intestine, and is cleaved to CO2 and NH3 by bacterial urease. This ammonia is partly lost in the feces and is partly reabsorbed into the blood.

In patients with kidney failure, plasma urea levels are elevated (hyperammonemia), promoting a greater transfer of urea from blood into the gut.

☆ Oral administration of neomycin reduces the number of intestinal bacteria responsible for this NH_3 production.


Mitochondria
(CPS-1) carbamoyl phosphate synthetase I
Free ammonia
NH_3
+
Co_2 + 2ATP
carbamoyl phosphate
+
ornithine
Allosteric Activator
N- Acetyl - glutamate
citrulline
citrulline + Aspartate
ATP
Arginosuccinate
AMP + PPi
pyrophosphate
fumarate
continue Krebs cycle
Arginine
Arginase
only in liver
ornithine
+
urea

Overall stoichiometry of the urea cycle

Free ammonia

$$\text{Aspartate} + NH_3 + CO_2 + 3ATP \longrightarrow \text{Urea} + \text{fumarate} + 2ADP + AMP + 2\,Pi + PPi + 3\,H_2O$$

- the synthesis of urea is irreversible, with a large, negative ΔG.

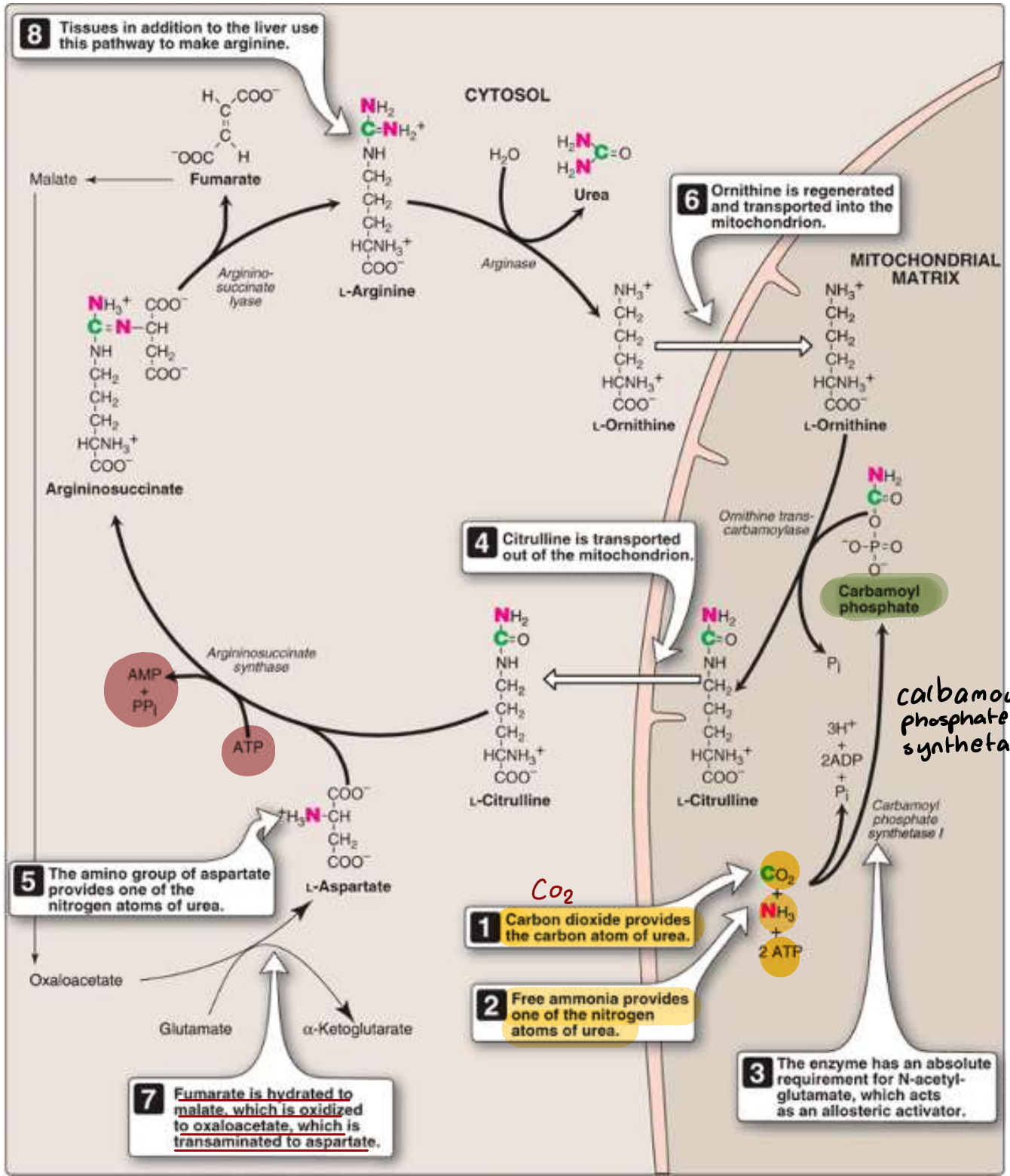
Regulation of the urea cycle

Acetyl-CoA + glutamate = N-Acetyl-glutamate

- N-Acetylglutamate is an essential activator for carbamoyl phosphate synthetase I (the rate-limiting step in the urea cycle) (synthesized from acetyl CoA and glutamate using arginine as an activator).
- the intrahepatic concentration of N-acetylglutamate increases after ingestion of a protein-rich meal, which provides both the substrate (glutamate) and the regulator of N-acetylglutamate synthesis.
- This leads to an increased rate of urea synthesis.

$$\uparrow Arginine \rightarrow \uparrow N-acetylglutamate \rightarrow \uparrow CPS\ I\ activity \rightarrow \uparrow Urea\ synthesis$$

- **Rate-limiting enzyme of urea cycle:** CPS I
- **Activator of CPS I:** N-acetylglutamate
- **Activator of NAG synthesis:** Arginine


8 Tissues in addition to the liver use this pathway to make arginine.
CYTOSOL
MITOCHONDRIAL MATRIX
Malate
Fumarate
L-Arginine
Urea
Arginino-succinate lyase
Arginase
6 Ornithine is regenerated and transported into the mitochondrion.
L-Ornithine
L-Ornithine
Argininosuccinate
4 Citrulline is transported out of the mitochondrion.
Ornithine trans-carbamoylase
Carbamoyl phosphate
Argininosuccinate synthase
AMP + PPi
ATP
L-Citrulline
L-Citrulline
Pi
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
carbamoyl phosphate synthetase 1
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
L-Aspartate
Oxaloacetate
Glutamate
α-Ketoglutarate
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.
CO2
1 Carbon dioxide provides the carbon atom of urea.
2 Free ammonia provides one of the nitrogen atoms of urea.
CO2 + NH3 + 2 ATP
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.
N-acetyl-glutamate
(Allosteric activator)

Which is incorrect about urea cycle:

1. ○ It occurs exclusively in the liver to produce urea
2. ○ The nitrogen's of urea molecule are supplied by free ammonia and aspartate
3. ○ The rate limiting enzyme is carbamoyl phosphate synthetase I
4. ◉ Oral administration of neomycin inhibits urea cycle in renal failure patients
5. ○ Ornithine is synthesized from arginine in the liver

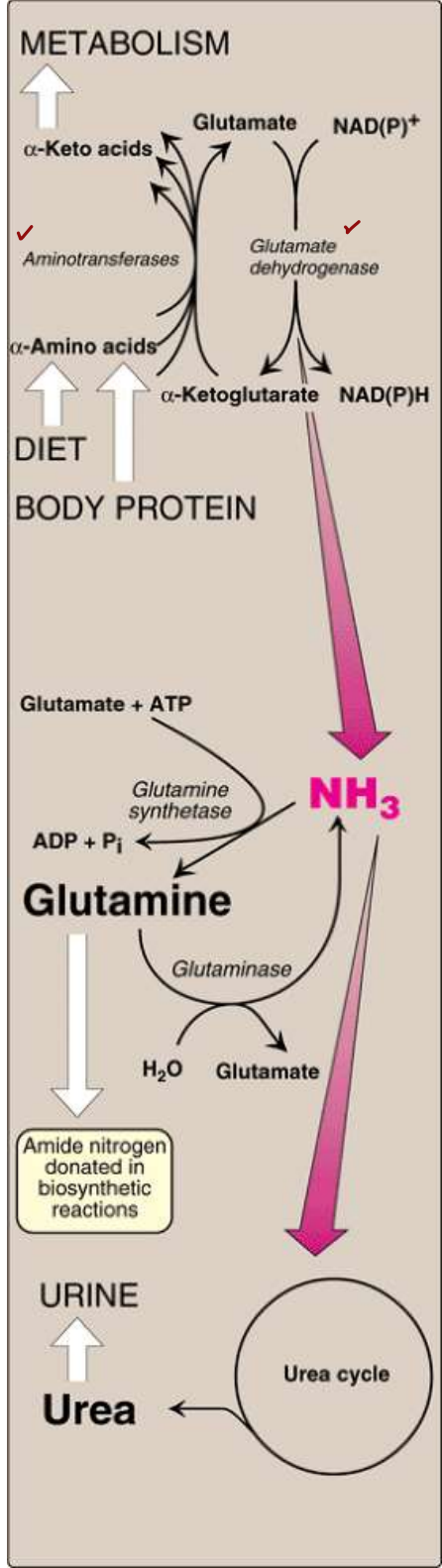
Next

إضافة ملاحظة

Metabolism of ammonia

- Slight increase in the concentration of urea in blood leads to hyperammonemia which is toxic to the CNS

- Sources of ammonia:
  - From amino acids: mainly in liver by the aminotransferase and glutamate dehydrogenase reactions
  - From glutamine: The kidneys form ammonia from glutamine by the action of renal glutaminase. Ammonia is also obtained from the hydrolysis of glutamine by intestinal glutaminase.
  - From bacterial action in the intestine: Ammonia is formed from urea by the action of bacterial urease in the lumen of the intestine.
  - From amines: Amines obtained from the diet, and monoamines that serve as hormones or neurotransmitters
  - From the catabolism of purines and pyrimidines



Transport of ammonia in circulation

As urea

As glutamine

- As **urea**: the most disposal form of ammonia which moves from liver to the kidney

- As **Glutamine**:
  - Occurs primarily in the muscle and liver and nervous system.
  - Circulating glutamine is removed by the kidneys and deaminated by glutaminase.

Hyperammonemia

- when the liver function is compromised, due either to genetic defects of the urea cycle, or liver disease, blood levels can rise above 1000 µmol/L.
- hyperammonemia is a medical emergency, because ammonia has a direct neurotoxic effect on the CNS (tremors, slurring of speech, somnolence, vomiting, cerebral edema, and blurring of vision).
- At high concentrations, ammonia can cause coma and death.

hyperammonia

Acquired

أسباب

- viral hepatitis
- ischemia
- hepatotoxins
- cirrhosis → - Alcoholism
  - hepatits
  - biliary obstruction

result in collateral circulation around the liver

hereditary

most common disorder:

Ornithine transcarbamoylase deficiency

- X linked
- affects men predominantly

but most urea cycle disorders are autosomal recessive

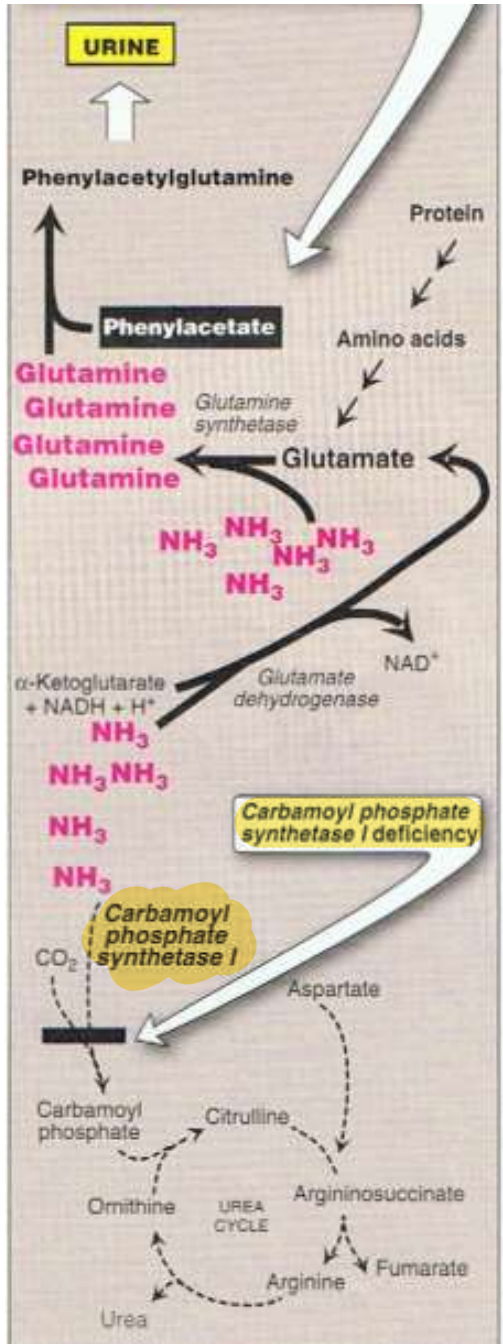
Hyperammonemia

- **Acquired hyperammonemia**: It may be due to viral hepatitis, ischemia, or hepatotoxins. Cirrhosis of the liver caused by alcoholism, hepatitis, or biliary obstruction may result in formation of collateral circulation around the liver.

- **Hereditary hyperammonemia**: Genetic deficiencies of each of the five enzymes of the urea cycle had an overall prevalence estimated to be 1 in 30,000 live births.
  - Ornithine transcarbamoylase deficiency, which is X-linked, is the most common of these disorders, affecting males predominantly

OTC deficiency

  - All of the other urea cycle disorders follow an autosomal recessive inheritance pattern. The failure to synthesize urea leads to hyperammonemia during the first weeks following birth leading to mental retardation
  - Treatment includes:
    - limiting protein in the diet
    - administering compounds that bind covalently to amino acids, producing nitrogen-containing molecules that are excreted in the urine (phenylbutyrate given orally is converted to phenylacetate)



جابت سؤال عن العامل الوراثي وكان بدها شو الخطأ

- **Hereditary hyperammonemia**: Genetic deficiencies of each of the five enzymes of the urea cycle had an overall prevalence estimated to be 1 in 30,000 live births.
- Ornithine transcarbamoylase deficiency, which is X-linked, is the most common of these disorders, affecting males predominantly
- All of the other urea cycle disorders follow an autosomal recessive inheritance pattern. The failure to synthesize urea leads to hyperammonemia during the first weeks following birth leading to mental retardation
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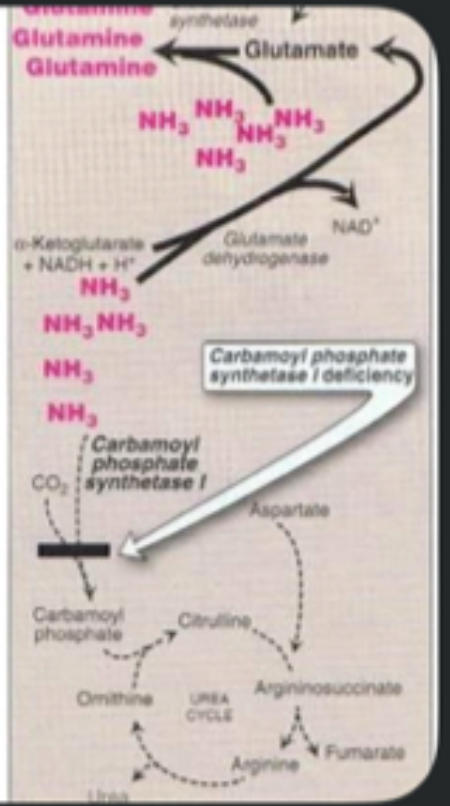


Which of the following statements is **INCORRECT** regarding hereditary hyperammonemia?

A. Deficiencies of urea cycle enzymes can lead to hyperammonemia in newborns
B. Ornithine transcarbamoylase deficiency is X-linked and most common
C. All urea cycle disorders are inherited in an autosomal recessive pattern
D. Failure of urea synthesis leads to accumulation of ammonia

Answer: C
✓ Incorrect because **OTC deficiency is X-linked**, not autosomal recessive.

- ال slides 11 الي ضلوا افضل طريقه لدراستهم انه chat يشرحهم و أنتم تلخصوهم بأيدكم على ورق ليثبتوا بالتوفيق

لكزوا
glucogenic
or
Ketogenic

a.a forms

oxaloacetate

↳ glucogenic a.a

Asparagine —(Asparaginase)→ Asparatate + NH_3

Asparatate —(transamination: α-Ketoglutarate → oxaloacetate; Aspartate aminotransferase)→ oxaloacetate + glutamate

a.a forms

α - Ketoglutarate

↳ glucogenic a.a

Glutamine —(glutaminase)→ glutamate + NH_3 (urea cycle) —(transamination)→ α-Ketoglutarate

oxidative deamination (glutamate dehydrogenase) release free ammonia + NH_3

proline —(oxidized)→ glutamate → α-Ketoglutarate

Arginine → ornithine → α-Ketoglutarate

Arginase (only in liver)

Histadine —(Histadase, oxidative deamination)→ urocanic acid → N-faminoglutamate (FIGlu) —(donate formimino group; tetrahydrofolate THF)→ glutamate → α-Ketoglutarate

Folate deficiency → FIGlu excretion test

Folic acid

a.a forms

pyruvate

↳ glucogenic a.a

Alanine ⇄ (NH_3) pyruvate

+ α.KG ⇄ (transamination, ALT) glutamate

Serine → Glycine → $CO_2 + NH_4^+$

Glycine + methylene group → Serine

Glycine: N5, N10-methylene THF

Serine —(serine dehydrogenase)→ pyruvate

Cysline —(reduction: H + NADH → NAD^+)→ Cysteine —(desulfuration)→ pyruvate

Therionine → pyruvate

Therionine → [redacted] → succinyl-CoA

α-Ketobutyrate

a.a forms **fumarate**

↳ hybird (glucogenic + Ketogenic)

phenylalanine —(hydroxylation; phenylalanine hydroxylase (PAH))→ Tyrosine → fumarate + acetoacetate

tetrahydrobiopterin + O_2

↳ co factor

a.a forms **Succinyl-CoA**

↳ glucogenic

methionine → SAM —(donate methyl group)→ homocysteine → atherosderotic vascular disease

a.a forms succinyl-CoA

↳ glucogenic

in muscles

valine + isoleucine → succinyl-CoA

threonine → [redacted] → propinoyl-CoA

dehydrated

α-Ketobutyrate

a.a forms **Acetyl-CoA / acetoacetyl-CoA**

↳ Ketogenic a.a

Leucine → Acetyl-CoA + acetoacetyl-CoA

Isoleucine → acetyl-CoA + propionyl-CoA

Lysine → Acetoacetyl-CoA

↳ Does NOT undergo transamination first

Tryptophan → Alanine → pyruvate

Tryptophan → acetoacetyl

can become 8
- oxaloacetate
- α-Ketoglutarate
- pyruvate
- fumarate
- succinyl-CoA
- Acetyl-CoA or Acetoacetyl-CoA

Catabolism of the carbon skeleton

After removing the amino group

Amino acids that form oxaloacetate

glucogenic a.a

- Asparagine is hydrolyzed by asparaginase, liberating ammonia and aspartate

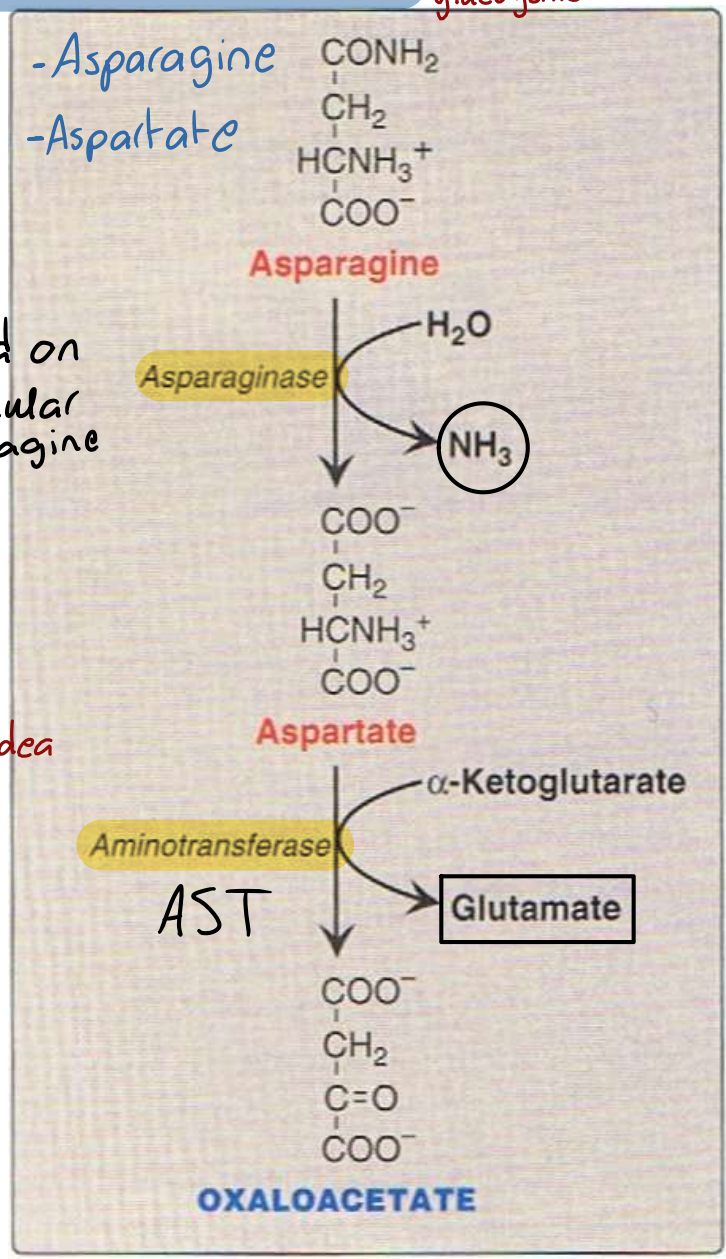
Asparagine $\xrightarrow{\text{Asparaginase}}$ Aspartate + NH_3

- Aspartate loses its amino group by transamination to form oxaloacetate

- Some rapidly dividing leukemic cells (cancer of blood cells) are unable to synthesize sufficient asparagine to support their growth. This makes asparagine an essential amino acid for these cells.
  - ↳ can't be synthesized by the body
  - depend on extracellular Asparagine

- Asparaginase can be administered systemically to treat leukemic patients.
  - ↳ so it destroys Asparagine and these cells starve and die

therapeutic idea



Amino acids that form α-ketoglutarate

major transport form of ammonia

1. **Glutamine** is converted to glutamate and ammonia by the enzyme glutaminase. Glutamate is converted to α-ketoglutarate by transamination, or through oxidative deamination by glutamate dehydrogenase.

2. **Proline** is oxidized to glutamate. Glutamate is transaminated or oxidatively deaminated to form α-ketoglutarate.

3. **Arginine** is cleaved by arginase to produce ornithine (occurs primarily in the liver). Ornithine is subsequently converted to α-ketoglutarate.

+ ornithine

Amino acids that form α-ketoglutarate

4. **Histidine** is oxidatively deaminated by histidase to urocanic acid. which subsequently forms N-formiminoglutamate (FIGlu). FIGlu donates its formimino group to tetrahydrofolate, leaving glutamate.

Folate

- Individuals deficient in folic acid excrete increased amounts of FIGlu in the urine (after ingestion of a large dose of histidine). The FIGlu excretion test has been used in diagnosing a deficiency of folic acid.

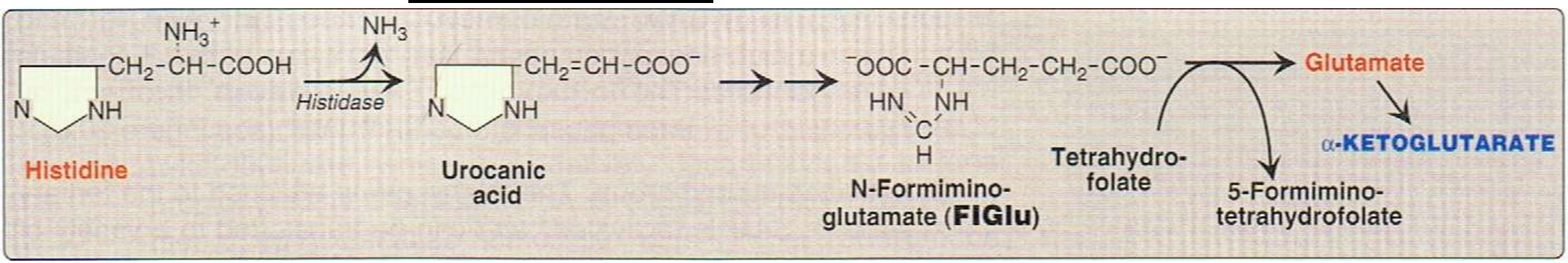
Why is Folate Important Here?

Because:

THF is required for proper FIGlu metabolism

If folate is deficient:

- FIGlu cannot transfer its group efficiently
- FIGlu accumulates
- excess FIGlu appears in urine



Amino acids that form α–ketoglutarate upon degradation include all the following except:

1. ○ Glutamine
2. ● Serine
3. ○ Arginine
4. ○ Histidine
5. ○ Proline

All amino acid that form a- ketoglutarate , except tryptophan الجواب

Important Integration: Glucose-Alanine Cycle

Muscle:

- sends alanine to liver
- liver converts alanine → pyruvate
- pyruvate used for gluconeogenesis

This transports:

- nitrogen safely
- carbon skeletons for glucose production

Amino acids that form pyruvate

1. **Alanine** loses its amino group by transamination to form pyruvate

2. **Serine** can be converted to glycine and N5,N10-methylenetetra-hydrofolate. Serine can also be converted to pyruvate by serine dehydratase.

3. **Glycine** can either be converted to serine by addition of a methylene group from N5,N10-methylenetetrahydrofolic acid, or oxidized to CO_2 and NH_4^+

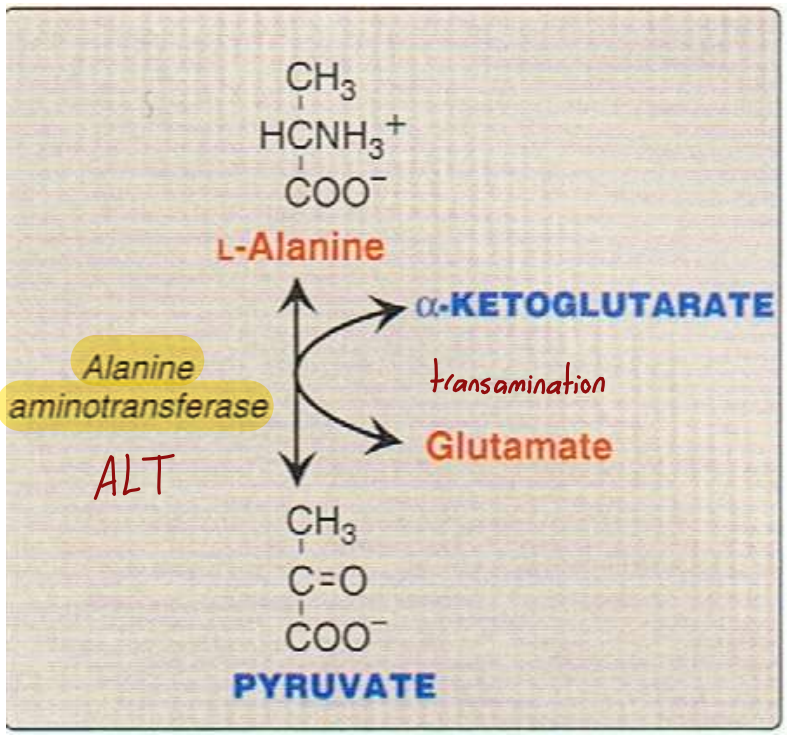
oxidized
NADH → NAD +

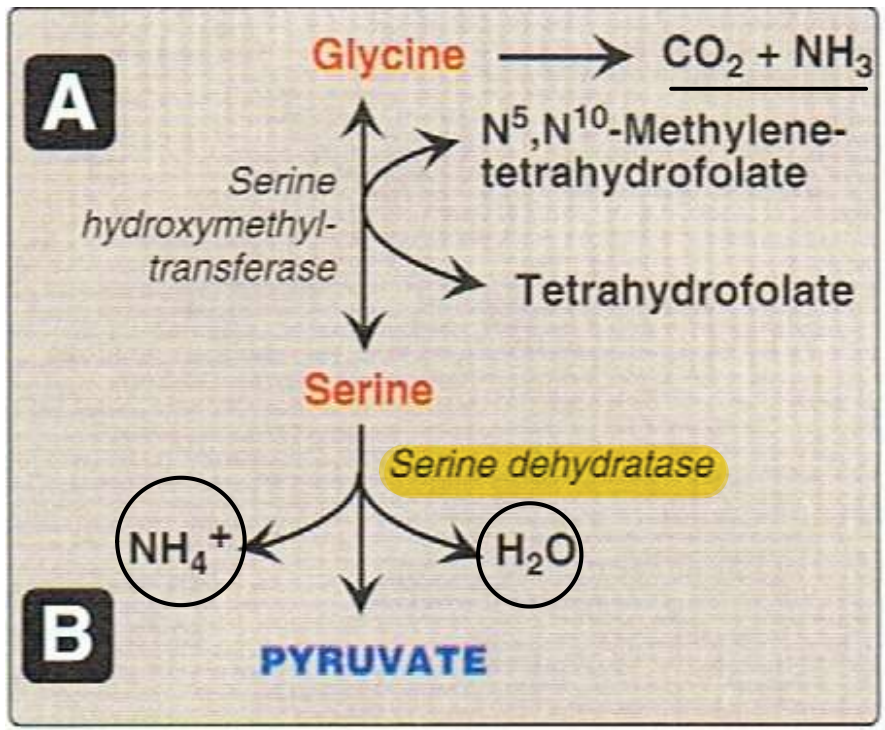
4. **Cystine** is reduced to cysteine, using NADH + H as a reductant. Cysteine undergoes desulfuration to yield pyruvate.

5. **Threonine** is converted to pyruvate or to α-ketobutyrate, which forms succinyl CoA.

Focus

Amino acids that form pyruvate





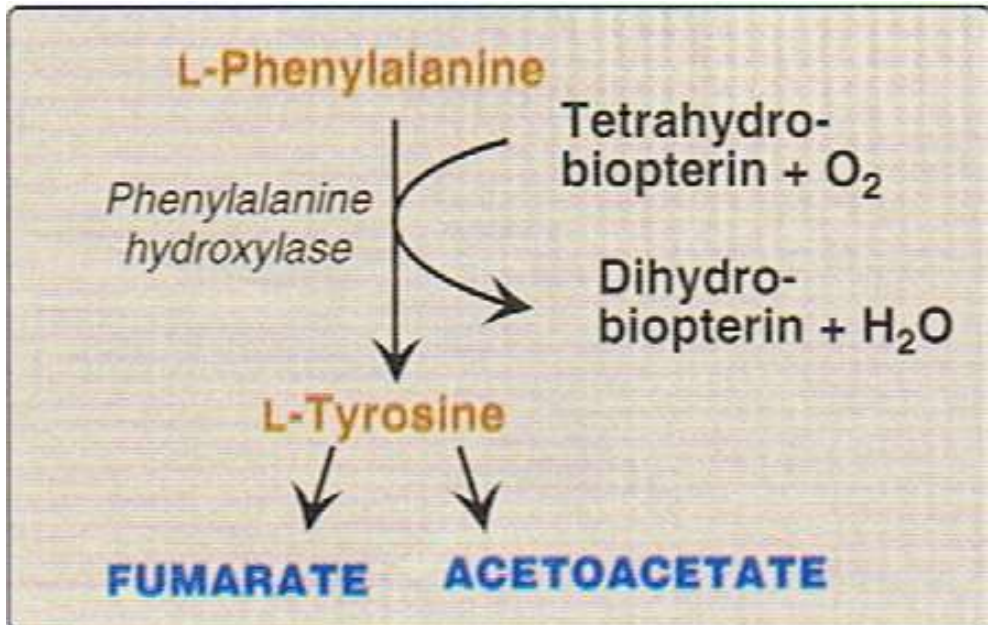
Amino acids that form fumarate

1. **Phenylalanine and tyrosine:** Hydroxylation of phenylalanine leads to the formation of tyrosine, which is catalyzed by phenylalanine hydroxylase. Thus, the metabolism of phenylalanine and tyrosine merge, leading ultimately to the formation of fumarate and acetoacetate. Phenylalanine and tyrosine are, therefore, both glucogenic and ketogenic.
2. Inherited deficiencies in the enzymes of phenylalanine and tyrosine metabolism lead to the diseases phenylketonuria and alkaptonuria, and the condition of albinism.

1- phenylKetonuria PKU

2- Alkaptonuria

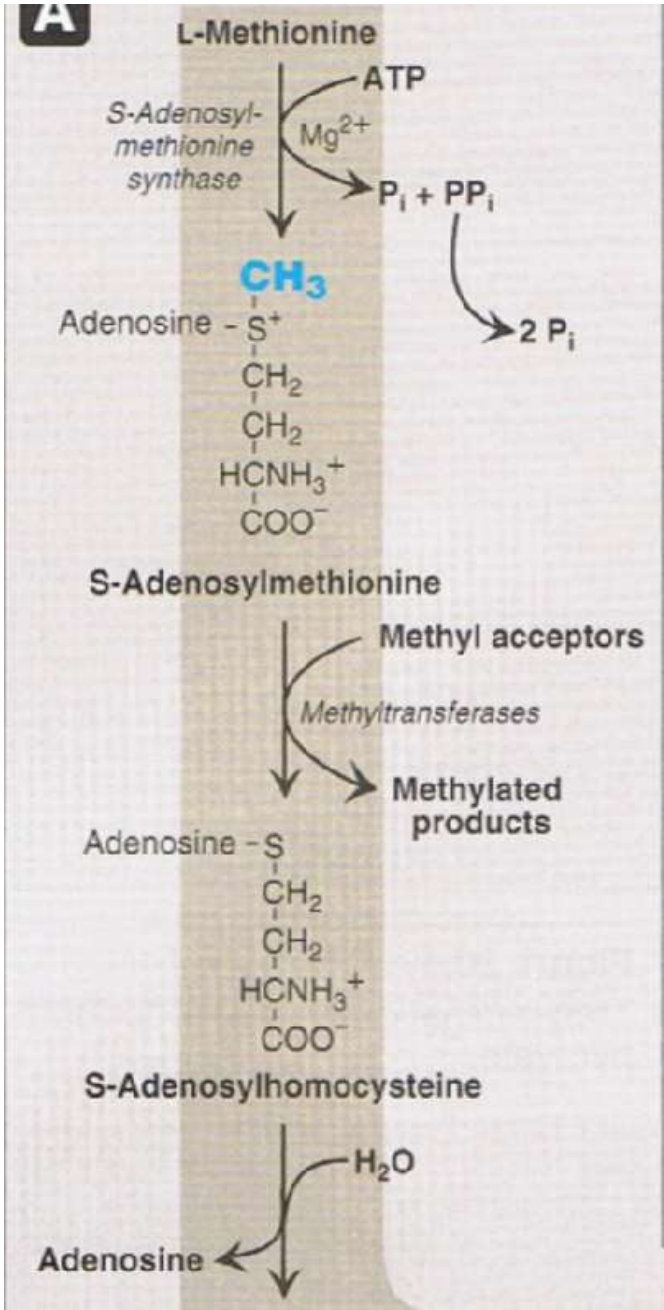
3- Albinism

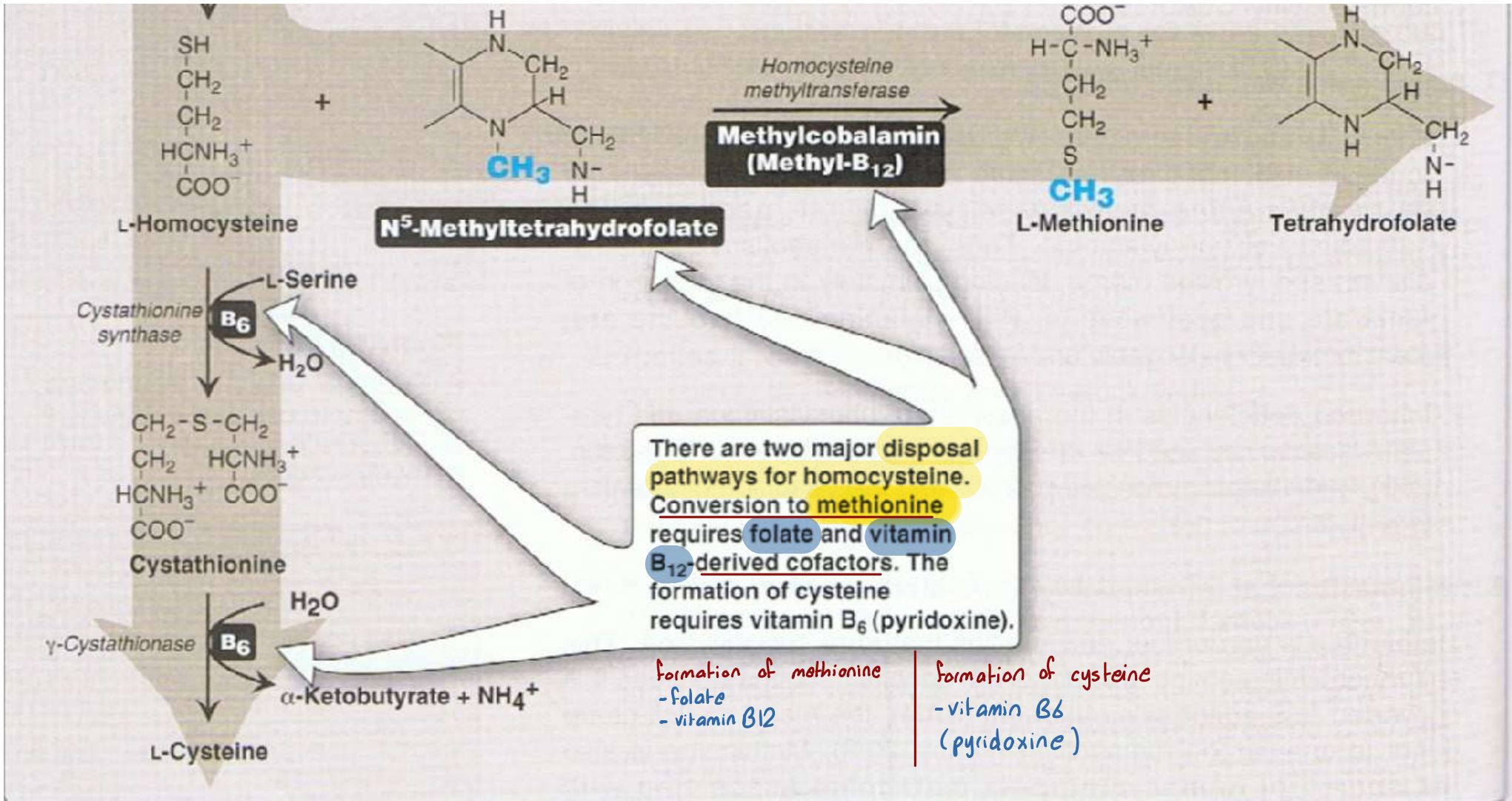


Amino acids that form succinyl CoA

- **Methionine:** Methionine is one of four amino acids that form succinyl CoA. This sulfur-containing amino acid deserves special attention because it is converted to S-adenosylmethionine (SAM), the major methyl-group donor in one-carbon metabolism

- Methionine is also the source of homocysteine, a metabolite associated with atherosclerotic vascular disease.




L-Homocysteine
N⁵-Methyltetrahydrofolate
Homocysteine methyltransferase
Methylcobalamin (Methyl-B12)
L-Methionine
Tetrahydrofolate
L-Serine
Cystathionine synthase
B6
H2O
Cystathionine
γ-Cystathionase
B6
H2O
α-Ketobutyrate + NH4+
L-Cysteine
There are two major disposal pathways for homocysteine. Conversion to methionine requires folate and vitamin B12-derived cofactors. The formation of cysteine requires vitamin B6 (pyridoxine).
formation of methionine
- folate
- vitamin B12
formation of cysteine
- vitamin B6 (pyridoxine)

Amino acids that form succinyl CoA

Degradation of valine, isoleucine, and threonine also results in the production of succinyl CoA- a TCA cycle intermediate and glucogenic compound.

1. Valine and isoleucine are branched-chain amino acids that yield succinyl CoA.

Focus

2. Threonine is dehydrated to a-ketobutyrate, which is converted to propionyl CoA, the precursor of succinyl CoA

3. Threonine can also be converted to pyruvate.

Amino acids that form acetyl CoA or acetoacetyl CoA

- Leucine, isoleucine, lysine, and Tryptophan form acetyl CoA or acetoacetyl CoA directly, without pyruvate serving as an intermediate (through the pyruvate dehydrogenase reaction.
- there are a total of six ketogenic amino acids.

1. **Leucine** is exclusively ketogenic in its catabolism, forming acetyl CoA and acetoacetate. Like other branched-chain amino acids, isoleucine and valine.

2. **Isoleucine:** is both ketogenic and glucogenic, because its metabolism yields acetyl CoA and propionyl CoA. The first three steps in the metabolism of isoleucine are virtually identical to the initial steps in the degradation of the other branched-chain amino acids. valine and leucine.

V.I

isoleucine ⟶ propionyl - CoA

Amino acids that form acetyl CoA or acetoacetyl CoA

3. **Lysine**, an exclusively ketogenic amino acid, is unusual in that neither of its amino groups undergoes transamination as the first step in catabolism. Lysine is ultimately converted to acetoacetyl CoA.
4. **Tryptophan** is both glucogenic and ketogenic because its metabolism yields alanine and acetoacetyl CoA.

exclusively Ketogenic	both Ketogenic & glucogenic
Leucine	Isoleucine
Lysine	tryptophan

Which of the following is does not match about amino acid metabolism

1-serine:pyruvate

2-tryptophan:[redacted] Acetyl-CoA

3-phenylalanine: acstoacstat

4-isoleucine: propyinle CoA

الاجابة: 3

Final Product	Amino Acids	Classification
Oxaloacetate (OAA)	Aspartate, Asparagine	Glucogenic
α-Ketoglutarate	Glutamate, Glutamine, Proline, Arginine, Histidine ornithine	Glucogenic
Pyruvate	Alanine, Serine, Glycine, Cysteine, Threonine, Tryptophan* → Alanine → pyruvate	Glucogenic
Fumarate	Phenylalanine, Tyrosine	Both glucogenic & ketogenic
Succinyl-CoA	Valine, Isoleucine, Methionine, Threonine	Glucogenic
Acetyl-CoA / Acetoacetyl-CoA	Leucine, Lysine, Isoleucine, Tryptophan, → propionyl-COA	Ketogenic or both

All of the following processes is execlosiv to liver except:

1-ketone body liver

2-urea cycle liver

3- bile acid synthesis liver

4-oxidative diamination liver / Kidney

5-phosphorletion of glycerol liver